"Researches on Tetanus.—Preliminary Communication." By Professor HANS MEYER and Dr. F. RANSOM. Communicated by Professor E. H. STARLING, F.R.S. Received May 7,—Read May 28, 1903.

(From the Pharmacological Laboratory of the University of Marburg.)

In the following communication we propose to give shortly the results of a series of experiments carried out with the object of throwing light upon certain points in the etiology of tetanus.

In the first place we directed our attention to so-called *local tetanus*, for which an experimental explanation was hitherto wanting.

Our observations led us further to a satisfactory interpretation of the *period of incubation;* to the discovery of a form of tetanus, confined to the sensory system, which we have called tetanus dolorosus; to a *theory of the action* of tetanus toxine and, finally, to a definition of the sphere within which the *serum treatment* of tetanus is effectual.

I.—*Local Tetanus.*

Gumprecht, in attempting an explanation of local tetanus, arrived *per exclusionem* at the conviction that the toxine is carried to the nervous centres by the nerve lymphatics, and Marie, also without positive proof, adopted the same theory. On the other hand, *Courmont* and *Doyon* and especially *Brunner* discussed, but did not accept this idea.

We have, as we believe, succeeded in demonstrating that the transport of tetanus toxine to the central nervous system takes place only by *way of the motor nerves.*

The experimental proof of this statement is as follows:—

1. Toxine was found in the *motor nerve* after subcutaneous injection in a hind leg. This result has been confirmed by *Marie* and *Morax.*

2. The endangered spinal centres can be protected, if the passage of toxine along the motor nerve be blocked by means of anti-toxine injected into the substance of the nerve. This holds good as well when the toxine has been injected locally as when it has been introduced direct into the blood.

3. If a lethal dose of tetanus toxine be injected into the n. ischiadicus of a cat, the first symptom is a local tetanus of the muscles of the injected limb. This is followed seriatim, after a certain period during which the other hind leg is usually attacked, by tetanus of the trunk, fore legs, muscles of the neck. Such a progression of the disease from the hinder to the front part of an animal can, under certain conditions, be prevented by *section of the spinal cord.*

4. A dose of toxine which, if introduced under the skin, causes no,

or but slight, symptoms, is often sufficient to produce death if injected into a motor nerve.

5. Even when the blood contains a large quantity of anti-toxine it is still possible to produce tetanus by injecting toxine into a motor nerve, although, under similar circumstances, subcutaneous or intravenous injections calls forth no symptoms whatever.

II.—*The Period of Incubation.*

If the path of the toxine is centripetal along the motor nerve, we should expect that injection direct into the substance of the nerve trunk would shorten the period of incubation.

If it were possible to introduce the toxine at once into the neighbourhood of the susceptible centres of the spinal nervous system, this shortening ought to be still more marked.

Both these anticipations are strikingly confirmed by our experiments. We are, therefore, of opinion that the greater part of the *period of incubation* is the expression of the time occupied in the conveyance of the toxine from the periphery along the motor nerves to the susceptible centres.

The results of our injections of toxine into the spinal cord are furthermore of great interest in that they prove that not only the exaggeration of the reflexes, but also the so characteristic *tetanic rigidity* of the muscles is due to the action of the toxine on the *nervous centres to the entire exclusion of the periphery.*

III.—*Tetanus Dolorosus.*

In all our experiments with injection of tetanus toxine into the substance of the spinal cord we observed, as the first symptom of intoxication, an extremely remarkable sensory disturbance which remained strictly localised, even when the muscular rigidity and the exaggeration of the reflexes were becoming general. In several cases, indeed, this sensory disturbance was so great as to lead to death, apparently from exhaustion, before the ordinary symptoms of tetanus were clearly developed.

Briefly, this symptom consisted in *extreme hyperæsthesia* of some part of the periphery corresponding to the spinal centre into which the injection had been made. This over-irritability of the pain-reflex apparatus is certainly due to the action of the toxine and is quite apart from the ordinary tactile-motor reflex tetanus. It never occurs after simple subcutaneous or intravenous administration of the toxine, nor after injection into a nerve trunk. On the other hand, if the toxine be introduced direct into a *posterior root* the result is pure *tetanus dolorosus*, thus indicating that the spinal ganglion forms an *insuperable obstacle* to the transport of the toxine.

The reflex answer to the attacks of pain consists in co-ordinated defence movements, *i.e.*, brain reflexes.

We draw from these experiments the following conclusions:—

1. The tetanus toxine never reaches the spinal centres by way of the sensory nerves.

2. The pain apparatus in the spinal cord is so insulated from the motor that an intoxication of the one group never goes over to the other.

3. The actual movement of toxine in the nervous system takes place *not in the lymphatics* but in the *protoplasm of the nerves.*

In the third conclusion is to be found the explanation of the fact that the cerebral tetanus of *Roux* and *Borrel* only occurs when the toxine is injected into (or by some lesion can reach) the brain substance. Between the brain and the peripheral nerves enough ganglia are interposed to bar the access of toxine to the convulsion centres.

The occurrence of tetanus dolorosus and cerebral tetanus would alone suffice to show that the toxine does not enter the nerve cells from the blood-lymph stream.

In the course of our researches on tetanus dolorosus we observed a peculiar condition which set in after division of the spinal cord. So soon as the communication with the brain was cut off, the manifestations of pain ceased of course, but, instead, a state of things developed which may be called *jactation tetanus*, the hind legs being kept almost uninterruptedly in jerking movement for hours together, till finally death occurred, apparently from extreme exhaustion.

As long as the pain-impulse could reach the brain there was no sign of this agitation, on the contrary, the animals kept as still as possible, in order to avoid any irritation of the hyperæsthetic area. But, transmission to the brain being prevented, the energy set free by the pain-stimulant discharged itself in the spinal cord, causing these movements, which may be looked upon as the *spinal equivalent* of the central reflex movements of the intact animal.

IV.—*Behaviour of Tetanus Toxine towards Sensory and Vasomotor Nerves.*

Injection of toxine into the infra-orbital nerve did not give rise to any symptoms analogous to tetanus dolorosus, but was once followed, after the quite unusual incubation period of 14 days, by an isolated tetanus of the erector muscles of the ear on the injected side.

Our observations lead us to think that the toxine may possibly be carried centralwards in a sensory nerve, but that sensory disturbance cannot be caused in this way.

The injection of toxine into the vagus of dogs was followed, in two cases, by a considerable slowing of the pulse which, in one case, lasted some four weeks. The effect, though small in proportion to the dose, seems to indicate that the heart-retarding centres of the vagus are susceptible to tetanus toxine. Except after injection into the vagus we have never observed slowing of the pulse in tetanised animals.

V.—*Exaggerated Reflexes and Muscular Rigidity.*

Our experiments show conclusively that the tonic rigidity of the muscles and the exaggeration of the reflexes are due to entirely different and independent processes. Reflex tetanus is known to be a discontinuous series of contractions of short duration. The tetanic rigidity of the muscles, on the other hand, is a continuous and gradually increasing shortening, which may however regress. This shortening, when it has existed for 24—30 hours, is not affected by curare nor by section of the nerve.

As regards the exaggeration of the reflexes, the experiments demonstrate clearly that this is at first strictly localised in the sensory part of the reflex arc belonging to the rigid limb. It is as if this point in the spinal cord were alone poisoned by strychnine.

VI.—*A Theory of Experimental Tetanus Intoxication.*

A consideration of the observed facts has led us to adopt the following explanation of the course of experimental tetanus:—

The toxine is taken up from the point of injection by the motor nerves. Passing along these it reaches first the motor centres in the cord and excites there an *over-irritability*, so that the discharges, which in the norm only give rise to the so-called *muscular tone*, become abnormally strong (though not reaching the maximum at first). The extensors and flexors of the injected limb brace themselves more and more and in the hind limbs the extensors tend to overcome the flexors. This, however, takes place gradually, so that for a considerable time voluntary and reflex movements can be executed. In short it may be said that tetanic rigidity is an *intensified muscular tone in the affected limb*. This tetanic contraction or retraction of the muscles is dependent on sensory excitement only in so far as, according to *Hering*, *every* motor impulse is peripherogen. At bottom it arises from a *pathological condition* of the *motor apparatus* in the spinal cord.

The excess toxine is next carried in the fibres of the cord to the motor apparatus of the corresponding limb of the other side. After a time, and if enough toxine has been given, the nearest connected *sensory* apparatus of the reflex arc in the spinal cord is attacked, with the result that the general reflex movements following irritation of the

injected limb or its nerve are exaggerated, though from all other parts of the body only normal reflexes are excited.

If the intoxication proceeds further the motor tonus, as well as the increased reflex irritability spreads, and rigidity of almost all the striped muscles and general reflex tetanus set in.

The tetanus of warm-blooded animals consists, in fact, of two processes separated from each other both in time and space. Of these the one is primary, a motor intoxication: local muscular rigidity; the other, secondary, is a local sensory intoxication: a diffused reflex tetanus, starting from the intoxicated neuron.

VII.—*The Behaviour of Tetanus Anti-toxine in the Organism.*

We found in repeated experiments that when tetanus toxine was introduced direct into a motor nerve, anti-toxine, though present in large quantities in the blood, was unable to prevent the outbreak of the disease or even to hinder a fatal issue. This was the case both when large doses of anti-toxine were given before and after the toxine, as well as when an actively immunised animal was employed.

We conclude, therefore, that injected anti-toxine does not reach the substance of the nerve fibrils and centres, and that even with highly immunised animals the nevrons remain free from anti-toxine.

On the other hand, it has been shown that the cerebro-spinal fluid, and, therefore, the nerve lymph of an immunised animal contains anti-toxine, there remains, therefore, only the fibril plasma as carrier of the toxine. We are further inclined to think that, in face of the facts revealed by our researches, it is difficult to look upon the nervous system as the source of tetanus anti-toxine.

As regards the value of the serum treatment of tetanus, it is clear, from what has been said above, that any toxine which is already in the nerve substance, though not yet in the spinal cord, cannot be reached and neutralised by anti-toxine, whether given under the skin or direct into the blood. An attack corresponding to the amount of toxine absorbed by the nerves will infallibly break out and run its course in spite of the anti-toxine. On the other hand, the toxine still in the blood and lymph will be rendered harmless by an injection of anti-toxine, the absorption of fresh toxine from the infected wound hindered, and in this way an otherwise fatal result may be prevented and the life of a tetanus patient saved.

NOTE.—A full report of these researches will appear in Schmiedeberg's 'Archiv f. experiment. Pathologie und Pharmakologie.'